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Low Density Lipoprotein Apheresis for the Treatment of Familial Hypercholesterolemia

Carmen Moga, Christa Harstall

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Comments relative to the information in this paper are welcome and should be sent to:

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EXECUTIVE SUMMARY

Background

Familial hypercholesterolemia (FH) is a genetic autosomal dominant disorder that is manifested by increased levels of the proteins, such as low density lipoprotein (LDL) cholesterol, that carry atherogenic lipids in plasma. There are two forms of FH: heterozygous and homozygous. The heterozygous form is one of the most frequent metabolic disorders occurring in the general population (1:500), whereas the more severe homozygous form is much less common (1:1 million). Early diagnosis and life-long treatment is essential for patients with FH in order to reduce the risk of developing cardiovascular diseases early in life, increase life expectancy and improve quality of life. In Alberta, approximately three patients have homozygous FH, while the number of patients with heterozygous FH who are no longer responding to standard treatment (diet and drugs) is less than 300.

LDL apheresis is an invasive procedure that selectively removes LDL cholesterol and other atherogenic lipoproteins from the blood via an extracorporeal circulation device. Only one LDL apheresis program is currently offered in Canada. The program, which is located in Quebéc, uses the HELP system and has been in operation for two years.

Objectives

To present the current evidence on the safety and efficacy/effectiveness of using apheresis to lower the concentration of LDL cholesterol in patients with FH. The report focused on two selective LDL apheresis systems: the dextran sulfate cellulose (DSC) Liposorber and the heparin induced LDL precipitation (HELP) system. Both systems have market approval from Health Canada.

Results

Six controlled studies compared a combination of LDL apheresis (DSC system) and drug therapy with drug therapy alone. A further two studies compared the DSC and/or HELP system with other apheresis systems. All of the studies varied considerably in methodological details such as: standard drug therapy and pre- and post-measurements of lipid profiles.

The weak evidence suggested that the DSC Liposorber system, in combination with lipid lowering drug therapy, lowered LDL cholesterol levels in older patients (> 50 years of age) with severe FH when they were treated at least once every two weeks for a minimum of one year. The mean per cent decrease in LDL cholesterol levels ranged from 34% to 81%. However, the use of a combined therapy meant that the contribution of LDL apheresis to the treatment effect is unclear.

The two studies that compared the various LDL apheresis systems concluded that all of the systems (Immunoadsorption, Liposorber, HELP, Lipidifiltration) comparatively decreased the levels of LDL cholesterol (mean per cent decrease values ranged from 54% to 65%). The most commonly reported adverse effects associated with DSC and HELP were hypotension, nausea, and vomiting. All of the reported adverse effects were transient.

Conclusions and Future Considerations

The information obtained from the reviewed studies must be considered cautiously. Generalization of the results to a local context is challenging because none of the studies were conducted in Canada and most of them only used the DSC system. The decision to include LDL apheresis in the package of services for patients with FH is fraught with difficult economic and ethical considerations because of the significant costs associated with the procedure. Planning processes will need to weigh costs and access against the gravity of the disease, and the poor quality of life and life expectancy of patients with homozygous FH.

Multicentre, concurrently controlled studies with long-term follow-up are required to assess whether LDL apheresis is more effective than drug therapy or plasmapheresis, either alone or in combination with standard care, in treating patients with FH.

The effectiveness and safety of LDL apheresis in special categories of patients such as children, or pregnant or lactating women also needs to be evaluated. Randomized crossover studies may be an appropriate study design to use since they avoid the ethical problem of treating patients who may require LDL apheresis. Cost benefit and cost effectiveness analyses are also needed to assess the economic consequences of using LDL apheresis instead of alternative treatments, such as drug therapy, plasmapheresis, or other LDL apheresis systems. The use of valid quality of life measures in these analyses is essential.

The establishment of a national registry for patients with FH and severe hyperlipidemia would be useful. This would allow tracking of reliable clinical outcomes for the various treatments and would assist in addressing long-term treatment issues for these severely ill patients.

Methodology

All original comparative studies published in English were identified by systematically searching PubMed, EMBASE, HealthStar, The Cochrane Library, Science Citation Index, and the web sites of various health technology assessment agencies, research registers, and guidelines sites from 1998 onwards.

ABBREVIATIONS

ACD: acid citrate dextrose

ACE: angiotensin converting enzyme inhibitors

ApoB: apolipoprotein B

CABG: coronary artery bypass grafting

CAD: coronary artery disease

CRP: C reactive protein

DALI: direct adsorption of lipids by hemoperfusion

DFPP: double filtration plasmapheresis

DSC: dextran sulfate cellulose

FDA: Food and Drug Administration (United States)

HC: hypercholesterolemia

FH: familial hypercholesterolemia

HDL: high density lipoprotein

HELP/LDL-A: heparin induced low density lipoprotein precipitation apheresis

HMG-CoA reductase: 3 hydroxy-3 methyl-glutaryl coenzyme A reductase inhibitors

HMZ: homozygous

HTZ: heterozygous

IMA: immunoadsorption

IVUS: intravascular ultrasound

LDL: low density lipoprotein

LDL-A: low density lipoprotein apheresis

LDL-C: low density lipoprotein cholesterol

Lp(a): lipoprotein (a)

MLD: minimal lumen diameter

PA: plaque area

pt: patient

PTCA: percutaneous transluminal coronary angioplasty

RCT – randomized controlled study

TAC: time averaged concentration

TC: total cholesterol

TG: triglyceride

VLDL: very low density lipoprotein

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SCOPE

This report (information paper) has been produced in response to a request from Capital Health for evidence on the safety and efficacy/effectiveness of apheresis in the lowering of low density lipoprotein cholesterol in patients with familial hypercholesterolemia. This report focuses on two selective low density lipoprotein (LDL) apheresis systems: the dextran sulfate cellulose (DSC) and the heparin induced LDL precipitation (HELP) systems. A comprehensive literature search was conducted and articles were selected using priori criteria (see Appendix A for methodology). The manufacturers of the two apheresis devices were contacted for technical and costing information. Clinicians who treat patients with familial hypercholesterolemia using apheresis were asked to provide an overview of their experiences. A draft of this report was reviewed by several leading Canadian experts.

BACKGROUND

Under normal conditions cholesterol is removed from the blood by low density lipoprotein (LDL) receptors. Hypercholesterolemia may be caused by overproduction of cholesterol or a removal defect or a combination of both.

Familial hypercholesterolemia (FH) is a genetic autosomal dominant disorder, caused by several mutations in the gene encoding the low density lipoprotein receptor [1] and characterized by a removal defect of the cholesterol/lipids from the plasma [2-6]. Over 700 mutations in the gene for the LDL receptor have been identified in patients with FH [5,7]. The frequency of these mutations varies considerably in different sub-populations.

The disorder is manifested by an increased level of proteins that carry lipids in plasma. Part of these lipids form a complex with the protein apolipoprotein B (apoB) present on low density lipoprotein (LDL), intermediate density lipoprotein, very low density lipoprotein (VLDL), and lipoprotein (a) (Lp(a)). Presence of these lipoproteins are considered to be important risk factors for the premature development of atherosclerosis, especially the increased levels of LDL that may favor LDL oxidation which plays a major role in atherogenesis. The higher the patient's LDL cholesterol level, the higher the coronary heart disease risk [4,8].

There are two forms of FH: heterozygous (HTZ) and homozygous (HMZ). In a person with HTZ FH half of the LDL receptors are absent or do not work properly and the rate of removal of LDL cholesterol (LDL-C) decreases substantially [3]. In a person with HMZ FH, LDL receptors are either absent (receptor-negative) or have only residual activity (receptor-defective).

Epidemiological and clinical aspects

World-wide there are estimated to be 10 million FH patients [9] but the prevalence of HMZ and HTZ forms vary. The HTZ form is one of the most frequent metabolic disorders in the general population (1:500) [1-3, 6, 10]. The disorder, however, is more prevalent in certain ethnic populations such as: French Canadians (1:200), Afrikaners in South Africa (1:70 to 1:100), Lebanese (1:171) and Johannesburg Jews (1:67) [3, 5, 6, 9]. While the HMZ form is much less common (occurs in approximately 1:1 million individuals), it is a more severe disease [5]. The plasma cholesterol concentrations are elevated two to three fold above average [3] in patients with HTZ and three to six above normal in HMZ [2, 3, 7, 10].

Most people with FH are underdiagnosed or only diagnosed after their first coronary event [9]. Homozygous FH usually comes to the attention of clinicians during infancy, due to the appearance of cutaneous and tendinous cholesterol deposits [2, 3, 5, 9] (xanthomas - a benign, fatty, fibrous, yellowish plaque, nodule or tumor that develops in the subcutaneous layer of skin often around tendons [11]; corneal arcus - a white or gray opaque ring in the corneal margin [12]) and premature coronary atherosclerosis. If untreated, patients may have manifestations of coronary artery disease (CAD) by the age of 10 years. Commonly described cardiovascular lesions include atherosclerosis of the ascending and descending aorta, and aortic and mitral valve stenosis or insufficiency. Death from myocardial infarction can occur as early as 3 years of age [13].

If untreated, heterozygous FH is manifested by the occurrence of premature CAD by the 5th decade for men and the 6th decade for women and is frequently fatal [2, 6, 7, 10]. Cutaneous and tendinous cholesterol deposits (xanthomas and xanthelasma – a soft, yellow spot or plaque usually occurring in groups on the eyelids) are present later, in adolescence. It is estimated that 200,000 HTZ FH patients die each year of preventable heart attacks [5].

A prompt diagnosis and aggressive treatment is critical to the long term survival of patients with FH. Therapies may include diet and drugs and, in addition, sometimes surgery, plasmapharesis and apheresis for the severe/selected cases.

Standard treatment

Diet alone can lower LDL-C by a maximum of 10% to 15%. This reduction is not considered to be clinically significant for the treatment for patients with HMZ and HTZ FH [14].

At present, there are several groups of drugs that can be used to lower high levels of cholesterol. These are bile-acid sequestrants (resins), nicotinic acid (niacin), fibric acid derivatives (fibrates) and HMG-CoA reductase inhibitors (statins). Statins currently provide the most dramatic reduction in plasma LDL-C levels when compared with other lipid reduction therapies [5, 6, 8, 9, 15]. Another promising drug, ezetimibe, belongs to a new class of drugs, cholesterol adsorption inhibitors, that appear to be effective; however its safety and tolerability has not yet been established in long term follow-up trials (beyond 12 weeks) [5, 16].

Hypercholesterolemia in FH patients is often resistant to a single drug therapy. Cholesterol levels may not normalize or decrease to target levels, even after combination therapy with two or three drugs [5, 7, 17, 18]. The prevailing majority of HTZ patients however, can be treated with diet and hypolipidemic drugs [2]. Patients with HMZ FH respond poorly to treatments known to be effective in patients with HTZ FH as HMZ patients produce fewer functional LDL receptors [3, 17, 19].

Alternative therapies

Several alternative therapies have shown varying levels of effectiveness. The porto-caval shunt procedure is an option but is associated with high morbidity and mortality and is only partially effective in lowering LDL-C [2, 3, 20, 21]. Liver transplantation has limited applicability and is associated with substantial risks and costs. In addition, recipients require life-long treatment with immunosuppressive drugs [2, 5, 21-23]. Gene therapy has been restricted to animal models and small pilot studies in humans. The results are less promising than other alternatives [3, 5, 17, 20, 22]. Partial ileal bypass of the ileum, in spite of being invasive and having side-effects, is a reversible procedure but has been found ineffective in patients with HMZ FH [2, 3, 10, 20, 21].

APHERESIS

When FH patients do not reach LDL-C target levels with drugs and, if they are in a high risk group (atherosclerotic cardiovascular disease), then plasmapheresis or apheresis may be indicated.

Low density lipoprotein apheresis (LDL-A) is an invasive procedure which selectively removes LDL and other atherogenic lipids from the blood using an extracorporeal circulation device. It is considered the "treatment of choice" for patients with HMZ or HTZ FH when all other treatment options have failed or when there is a drug intolerance [2, 7, 19, 21, 24-28]. LDL-A has been available since the early 1980s [29].

While LDL-A is a selective LDL procedure, plasmapheresis is a non selective procedure which acutely lowers the levels of both LDL and HDL cholesterol. The loss of HDL associated with plasmapheresis is undesirable (due to its role of protection against atherosclerotic diseases) and led to the development of selective LDL-A [13, 21]. Plasmapheresis is available in most centres where dialysis is being performed (personal communication, Dr. McCrindle).

The pioneers of selective LDL removal from the plasma include Lupien and colleagues of Quebec, Canada who developed a method in the 1970's that involved withdrawing a unit of blood, which was then mixed in a transfusion bag with heparin-agarose beads [21, 24, 30]. Both LDL and VLDL were selectively complexed with heparin-agarose; the blood was then reinfused through a transfusion filter that retained the beads. This method pointed the way to the current methods of selective LDL-A systems [21, 30].

LDL-A is used as primary prevention in patients with severe hypercholesterolemia (mainly HMZ) and as secondary prevention for patients with coronary heart disease and LDL-C levels greater than 200 mg/dL (or LDL-C>5.2 mmol/L) in conjunction with standard therapy. The treatment must be individualized based on the plasma LDL-C levels and administrated periodically, usually at one or 2-week intervals, for the entire life of the patient. The effect of the treatment depends on the pre- and post-treatment lipid levels and on the post-treatment level of returned lipids.

Treatment frequency can be established by measuring two parameters: the acute lowering of lipoproteins (the mean % decrease) and the time-averaged LDL-C value/concentration (TAC). The acute lowering of lipoproteins is determined by the difference in pre- and post- procedure lipid values as a per cent of the initial value. The TAC measurement takes into consideration the treatment frequency and the rate of rebound of the lipid level between treatments. TAC is a more sensitive measure but reported less frequently in published studies [7, 26, 31].

Table 1 presents the mean percentage decrease in lipoproteins, fibrinogen and C reactive protein in patients treated with the DSC Liposorber LA-15 system and the HELP system. Information was obtained from the literature and from representatives for the Kaneka Pharma America Co., New York (Liposorber LA-15) and B. Braun Medical Inc. (HELP). The level of reduction that is clinically relevant has yet to be determined [32]. After a single DSC apheresis treatment, the level of HDL-C is acutely reduced by 3% to 14% due to a process of dilution (during the blood return procedure, the plasma and cellular components that remain in the extracorporeal circuit (see Appendix B for detailed description of the DSC Liposorber LA-15 system) are returned to the patient with approximately 400 mL physiological saline solution). The pre-level of HDL-C may be increased by approximately 3 to 14% with the DSC system and by approximately 13% with the HELP system over the long term.

Table 1: Acute reduction in plasma lipids (%)

	Liposorber LA-15[1]			**HELP** [2, 3]		
	HMZ (n=5) LDL-C>500 mg/dL (LDL-C>13.0 mmol/L)	**HTZ (n=10)** LDL-C≥ 300-499 mg/dL (LDL-C≥7.8-12.9 mmol/l)	**Mean HMZ + HTZ**	**HMZ** LDL-C>500 mg/dL (LDL-C>13.0 mmol/L)	**HTZ** LDL-C≥ 300-499 mg/dL (LDL-C≥7.8-12.9 mmol/l)	**Mean HMZ + HTZ**
Total Cholesterol	71.6	63.3	61.0-71.0	57.3	51.9	52.7
LDL-Cholesterol	80.6	75.8	73.0-83.0	63.6	62.0	62.2
VLDL	73.5	69.0	47.0-68.0	N/A	N/A	52.0
HDL-Cholesterol	13.3	7.2	3.0-14.0	17.1	12.8	13.6
Lp(a)	65.3	67.7	53.0-76.0	N/A	N/A	55.0
Triglycerides	56.1	55.7	47.0-68.0	47.4	36.0	40.1
Fibrinogen	NA	N/A	29.0	64.9	58.7	58.0
C Reactive Protein	NA	N/A	50.0	N/A	N/A	50.0

NA – data not available

[1] Data are from the US multicentre (9 centres) clinical trial, 1988-1991 (FDA reviewed)

[2] Jaeger BR. Evidence for maximal treatment of atherosclerosis: drastic reduction of cholesterol and fibrinogen restores vascular homeostasis. *Ther Apher* 2001;5(3):207-211.

[3] Data from the US and the German multicentre (four US centres, nine German centres) clinical trial, 1989-1991 (FDA reviewed)

Description of LDL-A systems

At present, there are several LDL-A selective systems available such as: dextran sulfate cellulose LDL-A (DSC/LDL-A), heparin induced LDL precipitation (HELP/LDL-A), immunoadsorption LDL-A (IMA/LDL-A), and direct adsorption of lipids by hemoperfusion (DALI) (see Appendix B for detailed descriptions of each system). These selective LDL-A systems are seen to be superior to plasmapheresis and double filtration plasmapheresis (DFPP) procedures that are unselective and respectively semiselective. The LDL-A selective systems are considered to be more efficacious and safe and allow for the treatment of high risk patients with severe cardiovascular conditions and also pediatric patients [3, 31-33].

All of these systems, require systemic anticoagulation, process blood extracorporeally, and require venous vascular access. With the exception of the DALI system, all other LDL-A systems require the preliminary separation of the plasma from blood cells. Heparin is the anticoagulate used universally, but some systems can use other anticoagulation substances such as nafamostat mesilate (DSC) or a combination of heparin and acid citrate dextrose (Immunoadsorption and DALI).

All of the LDL-A systems, except for the DALI system, require approximately 60 minutes for set up. That time may vary depending on the skills of the operator. Only the Immunoadsorption system re-uses the columns for an average of 50 treatments. For all other systems the components of the equipment that were in contact with the patient's blood are discarded after each procedure.

The time per session of treatment varies between systems due to the volume of plasma processed and the rate of blood flow. The treatment time for the various systems differs from 1 to 2 hours for the HELP and DALI systems; to 2.5 to 3 hours for the DSC system; and 3 to 4 hours for the Immunoadsorption system. The Immunoadsorption and DALI systems are relatively new.

Both the DALI and DSC systems require an interruption of the administration of ACE-inhibitors (if the patient is on this drug) for at least 72 hours prior to each treatment due to the increased risk of developing anaphylactoid-like reactions (an acute severe type of allergic reaction).

Appendix C presents a table that details technical features of the DSC and HELP systems as they are the focus of this paper. This information was obtained from the manufacturers (personal communications, Kaneka Pharma America Co., New York and B. Braun Inc.).

REGULATORY STATUS

The DSC Liposorber LA-15 and the HELP systems received Class III licensing from Health Canada (date of issued October 2003 for the Liposorber LA-15 system and December 2001 for the HELP system). These licences do not restrict the use of either system but the manufacturers have specified some restrictions. The Liposorber LA-15 system is recommended to be used for children who weigh more than 15 kgs and are older than 5 years of age. The HELP system can be used for patients who weigh 37 kgs or more.

In Canada, medical devices are classified into four classes according to the rules of the risk-benefit classification system. Manufacturers need to obtain a licence for devices included in Class II, III, and IV. In order to obtain a Class III medical device licence, the manufacturers have to fill in an application form which requires information obtained from clinical studies on the safety and effectiveness of the device.

Both systems (the Liposorber LA-15 and the HELP) are also approved for use by the United States Food and Drug Administration (FDA). The FDA in 1996 approved the use of LDL-A DSC and in 1997, the FDA approved the HELP system. The Liposorber LA-40 did not receive approval for use in Canada or the United States (US) but it is distributed in Europe, the Middle East and Japan.

The indications for use of either system for the treatment of FH patients as specified by the Medical Devices Bureau, Health Canada, are similar to those specified in the documentation available from the manufacturers and the FDA. LDL-A should be used for the temporary acute removal of LDL-C from the plasma when diet has been ineffective and maximum drug therapy has either been ineffective or not tolerated in patients who are:

- functional hypercholesterolemic homozygotes with LDL-C>500mg/dL (or LDL-C>13.0 mmol/L);
- functional hypercholesterolemic heterozygotes with LDL-C≥ 300mg/dL (or LDL-C≥7.8 mmol/L); and
- functional hypercholesterolemic heterozygotes with LDL-C≥200mg/dL (or LDL-C≥5.2 mmol/L) and documented coronary heart disease.

The manufacturers of the Liposorber LA-15 system have requested physicians who are licensed to use the device in the US to report periodically patient data (clinical outcomes, adverse events and quality of life) for a registry [7, 20] (available: http://www.liposorber.com).

EVIDENCE OF EFFICACY/EFFECTIVENESS OF THE DSC SYSTEM AND THE HELP SYSTEM

No systematic reviews were found after searching the literature for studies published from 1998 to 2003. The best available research evidence is from non-randomized controlled studies which compared the results obtained using LDL-A with associated drug therapy with the results from patients who only received drug therapy [26, 34-37], one cross-over study [38] and one comparative study on the efficacy and safety of different LDL-A systems [39]. There were no controlled studies found that compared plasmapheresis with apheresis for patients with FH. An RCT published by Thompson et al. in 1995 was included [27].

Details from all the selected studies are presented in Appendix D.

Efficacy dextran sulfate cellulose adsorption system

Table 2 summarizes the results from the six controlled studies using the DSC system with drug therapy compared to drug therapy alone. Most of the studies were multicentre trials.

Table 2: Summary of controlled studies

Study	Device	Sample*	Results
Matsuzaki et al. [34] Period = 1 year **Treatment interval:** 2 weeks	DSC Liposorber LA-15 Kaneka Japan	N=18 C= 7 HTZ (54 years) E=11 HTZ (50 years)	C: LDL-C - minus 4% HTZ) E: LDL-C - 34% (HTZ)
Nishimura et al. [35] Period = 2.3 years **Treatment interval:** 17 days	DSC Liposorber Kaneka Japan	N=36 C=11 HTZ (51 years) E=25 HTZ (51years)	C: LDL-C - 34% (HTZ) E: LDL-C - 43% (HTZ)
Mabuchi et al. [26] Period = 6 years **Treatment interval:** 2 weeks	DSC Liposorber Kaneka Japan	N=130 C=87 HTZ (59 years) E=43 HTZ (57 years)	C: LDL-C - 28% (HTZ) E: LDL-C - 58% (HTZ)
Koga et al. [36] Period = 7.8 years **Treatment interval:** 2 weeks (HMZ); 2-4 weeks (HTZ)	DSC Kaneka Co.	N=21 C=10 HTZ (63 years) E=11 (2HMZ, 9 HTZ) (41 years)	C: LDL-C - 23% (HTZ) E: LDL-C - 61% (HMZ) 57% (HTZ)

C = control group; E = experimental group; N = total number of patients included; LDL-C mean % reduction; * mean age presented

Table 2: Summary of controlled studies (cont'd)

Study	Device	Sample*	Results
Gordon et al. [37] Period = 5 years **Treatment interval:** 11±5 days (HMZ) 14±6 days (HTZ)	DSC Liposorber LA-15 Kaneka Pharma America, New York	N=64 (first phase) C= 9 HTZ E= 10 HMZ, 45 HTZ	C: LDL-C - ? (HTZ) E: LDL-C - 81% (HMZ) 76% (HTZ)
Thompson et al. [27] Period = 2.1 years **Treatment interval:** 2 weeks	DSC Liposorber LA-15 Kaneka Japan	N=39 C=19 HTZ (50 years) E=20 HTZ (49 years)	C: LDL-C - 44% (HTZ) E: LDL-C - 66% (HTZ)

C = control group; E = experimental group; N = total number of patients included; LDL-C mean % reduction; * mean age presented

Matsuzaki et al. [34] conducted a multicentre trial with 18 HTZ patients with angiographically defined CAD. All patients were receiving drug therapy HMG-CoA reductase inhibitors at the time of commencing the study. Patients were assigned to one of two groups: 11 patients who were treated biweekly with LDL-A (DSC Liposorber LA-15 Kaneka Japan) plus medication and seven patients who received medication only. The aim of the study was to measure the effects of the treatments by assessing changes in the minimal lumen diameter (MLD) measured by coronary angiography and the level of plaque area (PA) by intravascular ultrasound (IVUS) technique. The LDL-A group showed 34.3% reduction in LDL-C levels after one year follow-up while the group receiving medication alone showed no changes in LDL-C levels. During the follow-up period, MLD was increased in the LDL-A group and was decreased in the medication group. PA was decreased in the LDL-A group but increased in the medication group. Significant differences were shown in net change in MLD ($P<0.004$) and PA ($P<0.008$) between both groups. The results suggested that aggressive lipid-lowering therapy using the combination of LDL-A and lipid-lowering drugs may induce regression of coronary atherosclerotic plaque in patients with HTZ FH.

In a prospective controlled study which involved 12 medical centres, **Nishimura et al.** [35] investigated the effect of intensive lipid lowering LDL-A in 36 HTZ FH patients. Twenty-five patients received LDL-A (DSC Liposorber Kaneka Japan) and cholesterol-lowering drug therapy (pravastatin, probucol, cholestyramine) and 11 patients received only drug therapy (pravastatin, probucol, cholestyramine). Significantly more patients on LDL-A showed regression or no change in coronary atherosclerosis compared with those on drugs alone ($p<0.004$). The main decrease from baseline in LDL-C in the drug group was 34% versus 43% in the LDL-A group. With regard to changes in coronary atherosclerotic lesions, in the drug group, 64% of the patients showed progression, none showed regression and 36% showed no change. On the other hand, in the LDL-A group, 8% of the patients showed progression, 16%

showed regression and 76% showed no change. Regression of lesions or suppression of progression was observed in 92% of the patients who received LDL-A ($p<0.004$). The conclusion of the authors was that intensive cholesterol lowering therapy with LDL-A associated with lipid lowering drugs can achieve a substantial decrease in LDL-C levels to induce regression of coronary lesions in HTZ FH patients with advanced CAD.

The **Mabuchi et al.** study [26] enrolled 130 HTZ FH patients with angiographically defined CAD, and treated 43 of them with drug therapy plus LDL-A (DSC Liposorber, Kaneka Japan) and the others 87 with drug therapy alone (statin, probucol, cholestyramine or fibrate) for a follow-up period of 6 years. In patients treated with apheresis and drug therapy, LDL-C was reduced by 58%, while in the group receiving only drug therapy LDL-C was reduced by only 28%. The study was not a randomized trial and patients allocated to treatment with LDL-A and drugs had significantly fewer smokers and a higher baseline of LDL-C than the patients receiving drug therapy. After adjusting for specific risk factors (excluding patients treated with coronary artery bypass grafting or smokers), the proportion of patients without any coronary events was significantly higher in the LDL-A group. Authors concluded that LDL-A with drug therapy is an effective treatment for coronary heart disease in patients with HTZ FH, and may become the therapy of choice in severe types of FH.

In the controlled study conducted by **Koga et al.** [36] 11 patients with severe FH (two HMZ and nine HTZ) who were treated with combined LDL-A (DSC Kaneka Co.) and cholesterol-lowering drug therapy (pravastatin or probucol) for a mean of 7.8 years were compared to 10 patients with mild HTZ FH who were treated with conventional cholesterol-lowering drugs (pravastatin or probucol) for a mean of 5.5 years. Study end-points were ultrasonographic changes of atheromatous plaque of the carotid artery and the annual progression rate of early carotid atherosclerosis. In HTZ patients, LDL-A associated with drug therapy caused reductions of 56.8% in LDL-C. In the group treated with conventional therapy the level of LDL-C was reduced by 22.9%. During the long-term treatment period, the existing plaque tended to progress and new plaque formation in carotid arteries was also observed in both groups but the annual progression rate of mean maximum intima-media thickness in the common carotid artery was significantly lower in the group treated with LDL-A, suggesting regression. However, the patients in the control group were considerably older (mean age 63 years versus 41 years in the apheresis group). The authors note that the results suggest that the long-term treatment with combined LDL-A and drugs may delay the progression of the atherosclerotic process and prompt the stabilization of atheromatous plaque in severe FH patients.

Gordon and colleagues [37] reported results from a multicentre study which examined the long term effects of LDL-A (DSC Liposorber LA-15, Kaneka Pharma America, New York) in a trial with a follow-up period of 5 years. The study consisted of a 22 week controlled treatment period including 54 patients with HTZ FH and ten patients with HMZ FH followed by an optional phase with 39 HTZ patients and 10 HMZ patients that included LDL-A therapy and lipid-lowering drug therapy (drugs not specified). Only 29 patients out of a total of 49 patients completed the optional phase.

The acute reductions in LDL-C and TC achieved with LDL-A in the initial treatment phase were maintained during long-term therapy. The main percentage of acute reduction in LDL-C was 76% per procedure in both HTZ and HMZ patients. The study was not designed originally to examine clinical outcomes and coronary angiography was not part of the protocol. Based on the results of this study the US Food and Drug Administration approved the use of LDL-A for patients who met the criteria for enrolment in the trial.

Only one randomized controlled multicentre study was published (in 1995). **Thompson and colleagues** [27] conducted the study and enrolled 39 HTZ FH patients. Twenty patients received LDL-A (DSC – Liposorber LA-15 Kaneka Japan) and cholesterol-lowering drug therapy (simvastatin) while 19 patients were treated with conventional drug therapy (simvastatin, colestipol). Quantitative coronary angiography was done in the 6 weeks before randomization and repeated at a mean of 2.1 years later. Changes in serum lipoproteins were similar in both groups apart from greater lowering of LDL-C by apheresis. There were no significant differences in primary angiographic endpoints per patient but lesion-based and segment-based secondary endpoints were more pronounced in the drug group. The authors concluded that LDL-A seemed to offer no advantage over combination drug therapy however, it does provide an alternative option for treating those HTZ patients with established coronary disease who are intolerant of, or unresponsive to, combination drug therapy. Kaneka (Germany) provided all of the apheresis equipment and disposables used in this trial.

Efficacy of different LDL-A systems (comparative studies)

Only two studies were located that compared the efficacy and safety of various LDL-A systems and these are summarized in brief in Table 3.

Table 3: Summary of device comparative studies

Study	Device	Sample*	Results
Richter et al. [39] Period = 4.6 years **Treatment interval:** weekly (30 patients) 2 weeks (4 patients)	Immunoadsorption Liposorber HELP	N=34 HTZ (47 years) n=18 n= 8 n= 8	LDL-C - 62% (HTZ) LDL-C - 65% (HTZ) LDL-C - 59% (HTZ)
Julius et al. [33] Period = 2 months (Part I+II) **Treatment interval:** weekly	Part I HELP Lipidfiltration-Cascadeflo AC-1770	N=5 HTZ (64 years) n=5 n=5	LDL-C - 54% (HTZ) LDL-C - 56% (HTZ)
	Part II HELP Lipidfiltration-Lipidfilter EC-50	N=6 HTZ (62 years) n=6 n=6	LDL-C - 61% (HTZ) LDL-C - 61% (HTZ)

N = total number of patients included; LDL-C mean % reduction; * mean age presented

Richter et al. [39] compared the efficacy of three LDL-A systems used to treat 34 HTZ FH patients for a mean follow-up of 4.6 years. The Immunoadsorption system was used in 18 patients, eight patients received the DSC and eight patients the HELP system. Apheresis was generally provided weekly. The decrease of lipoproteins was comparable with all three LDL-A systems. In order to evaluate the progress of coronary lesions, angiograms were performed for 23 patients. The results showed a regression of these lesions for four patients while the others registered a halt in progression. Stenosis did not progress to occlusion but remained open over the whole observation period. All patients reached comparable levels of cholesterol by the three LDL-A systems and no relevant difference in the course and outcome of coronary heart disease was observed, although some patients in each of the groups started drug therapy at different times during the study. The conclusion of the authors was that all three LDL-A systems were effective in lowering atherogenic lipoproteins.

Julius and colleagues [33] conducted a comparative cross-over study treating patients with the HELP and the Lipidfiltration (in first part Cascadeflo AC-1770 and in the second part Lipidfilter EC-50) systems. The first part of the study included five HTZ FH patients. Another patient was added in the second part of the study. Before entry in the study, all patients were treated with apheresis for a minimum of 2 years. LDL-A systems were compared intraindividually with regard to lowering and modifying plasma proteins. Both devices were safe and effective with respect to the extracorporeal removal of LDL-C, Lp(a), fibrinogen and change of LDL/HDL-C ratio while treating identical plasma volumes. Because there were no significant differences with respect to LDL-C reduction it was concluded that the choice of lipid apheresis system could be based on individual preferences.

EVIDENCE OF SAFETY AND CARDIOVASCULAR EVENTS

The safety of these systems were not mentioned in six out of the eight studies determining efficacy and effectiveness. Most of the studies reported long term events such as myocardial infarction and numbers of angioplasty procedures (see Tables 8 and 9, Appendix E).

LDL-A is a life long therapy that removes LDL and other lipids from the plasma. However, other components may be removed as well, such as the HDL fraction of lipids, different coagulation factors, minerals and vitamins. There are also some questions if long term LDL-A triggers on oxidation process [4, 40]. On the one hand, the apheresis therapy causes an oxidative stress by stimulating reactive oxygen species and the production of toxic peroxidation products like plasma hydroperoxides. Consequently, a deficiency in plasma antioxidants is reported. On the other hand, periodic treatment with LDL-A may attenuate the oxidation mechanism by increasing the removal of LDL (which have been reported to be highly susceptible to oxidation thus more atherogenic) and hydroperoxides, from the plasma. Some clinicians suggest that antioxidant vitamin supplements are required for FH patients who are on long-term LDL-A to counteract the continuous oxidative challenge [4]. Long-term treatment with an extracorporeal system may also cause iron deficiency anemia. This anemia, however, responds well to iron supplementation [18].

Short term adverse effects

Because both LDL-apheresis systems (DSC and HELP) require the administration of heparin during blood filtration, the procedure is contraindicated in patients with coagulation problems such as hemophilia and in patients who have had recent surgery or those that have hypersensitivity to heparin. In addition, apheresis using Liposorber LA-15 cannot be provided to patients with known hypersensitivity to ethylene oxide (present in the dextran sulfate columns of this device) [3].

Patients with low body weight have a tendency to develop hypotension and they need more attention when beginning LDL-A treatment. Psychological elements such as nervousness and anxiety concerning the treatment might cause vasovagal reactions with decreased circulatory blood volume. This seems often to be the case in patients when extracorporeal treatment is used for the first time [18].

Potential adverse reactions associated with DSC are similar to those expected with any procedures involving extracorporeal circulation: hypotension, nausea/vomiting, flushing/blotching, angina/chest pain, edema, etc. [3]. Patients on treatment with antihypertensive drugs (diuretics, calcium antagonists and especially angiotensin converting enzyme (ACE) inhibitors within the last 24 hours before LDL apheresis), are at risk of developing anaphylactoid-like reactions such as: hypotension, flushing, dyspnea, bradycardia or shock [7, 14, 18, 21, 29, 39, 41]. These reactions are mediated by bradykinin release and can be prevented by temporarily discontinuing ACE inhibitors (at least 72 hours before the LDL-A treatment), which impair bradykinin catabolism, or by changing the anticoagulant from heparin to nafamostat mesilate or changing the treatment from ACE inhibitors to angiotensin receptor II antagonist [14, 18, 42]. Further studies are needed to confirm the safety of these alternative approaches during LDL-A treatment.

The adverse effects most commonly associated with the HELP apheresis system include: vasovagal reactions, facial swelling, hypotension, angina, fatigue, nausea, vertigo, burning eyes, chills and shivering. HELP apheresis is compatible with ACE inhibitors, and there is no need to interrupt administration of these drugs before the apheresis treatment [3, 41, 43].

Information regarding adverse effects related to LDL-A was reported in two studies but as combined data (see Appendix E) [37, 39]. In these studies the most prevalent events were: hypotension, nausea and vomiting and problems with venous access and venous bleeding. Both systems may encounter problems with vascular access and malfunctioning of the equipment. All authors reported that the adverse reactions were transient and patients recovered quickly with proper treatment.

Long term effects

LDL-A lowering therapy associated with drug therapy seems to reduce the rate of future cardiovascular events represented by cardiac death, coronary revascularization procedures (CABG and PTCA), myocardial infarction or cerebrovascular events when compared with the groups receiving drug therapy alone. Since these events are rare and the patient populations are not the same in the groups, it is difficult to draw any conclusions about the effects of LDL-A in comparison to drug therapy alone. The table in Appendix E presents long term events observed in patients treated with DSC, HELP and other apheresis systems. It remains unclear whether the differences in the systems significantly affect their long term clinical outcomes.

COSTS

There is a lack of information in the literature regarding costs associated with operating apheresis systems. The estimated cost for treatment with either system (Liposorber, HELP) is influenced by the complexity of the devices, the single-use disposables (columns, tubing, filters and the other components of the system that have been in contact with the patient's blood are discarded) and treatment frequency. Most patients need treatments every two weeks on average (between 30 and 45 treatments per year), however, some patients will need treatment at more frequent intervals [14].

Information regarding the capital cost of the Liposorber LA-15 and the HELP devices, disposables, additional supplies and maintenance costs was received from the manufacturers (Kaneka Pharma America Co., New York and B. Braun Medical Inc). In addition, other costs such as training and indirect patient costs must be considered. The cost comparison for both devices is presented in Table 4.

Table 4: Cost comparisons of LDL-apheresis systems

	Liposorber LA-15 ($Cdn)	HELP ($Cdn)
Cost of equipment	45,776.50	39,237.00 + 7,847.40 (the dialysis equipment: Zyzatech Millennium M-750)
Disposables cost / procedure	1,765.67	1,177.11
Additional supplies	65.40 - 130.79	65.40 -130.79
Maintenance costs	no cost the first year, 3,923.70/year after that	no cost the first year, 3,923.70/year after that
Estimated cost/year/patient (for disposables+supplies)	95,215.64 - 98,615.92 (weekly) 47,607.82 - 49,307.96 (two weeks)	64,610.52 - 68,010.80 (weekly) 32,305.26 - 34,005.40 (two weeks)

Note: costs are provided in Canadian dollars
Conversion from US dollars: March 30, 2004, exchange rate (Bank of Canada): 1.3079
Information was obtained from: Kaneka Pharma America Co., New York (Liposorber LA-15) and B. Braun Medical Inc. (HELP)

Usually, after an LDL-A the cholesterol level is kept in the ideal range only for a few days (3 to 5) even in HTZ FH patients [30]. In the first week after apheresis the increase of the LDL-C level is linear but the rebound is less rapid during the second week [39]. In most patients, the peak total and LDL-C levels seen at two weeks after the initial apheresis are lower than the values prior to apheresis. In some patients (especially HMZ) it may be necessary to increase the number of treatments because of the rapid rebound of the cholesterol level [3, 30].

One comparative study reported a cost-consequence analysis [44]. The results of three therapies LDL-A, CABG, PTCA were compared in terms of effectiveness in the treatment of coronary artery disease. The conclusion was that LDL apheresis using Liposorber LA-15 may be a good strategy for treating coronary disease if its cost can be improved.

Antecubital veins can be used as chronic vascular access in approximately 70% of patients, while 30% need surgical construction of an arteriovenous fistula at the forearm [41]. These interventions may add other costs to the total cost of the procedure.

In addition to LDL-lowering and regression of atherosclerotic plaque, other effects that may impact a cost-effectiveness analysis include: decrease blood viscosity and improved blood rheology [7, 29, 41, 43, 45-50]; improved coronary microcirculation and relief from ischemic symptoms [7, 43, 50-52]; lowered oxidized LDL levels [7, 32, 40, 46]; down-regulation of leukocyte and endothelial adhesion molecules [7]. Both systems (DSC and HELP) might be beneficial for long-term treatment in patients with moderately elevated serum fibrinogen [43, 45, 51]. C reactive protein (CRP) was effectively removed by DSC and HELP systems. Decrease in CRP plasma levels may be involved in the prevention or regression of atherosclerotic vascular diseases [29, 45, 49, 50, 53]. The coagulation factors VIII, V, VII and X as well as fibronectin and von Willebrand factor are reduced during DSC LDL-A. Short-term improvements with LDL-A treatment are probably due to amelioration of hemorheology as a result of reduced plasma viscosity. Morphologic improvements of coronary or peripheral arteries can only be expected after approximately 2 years of intensive treatment [41, 51].

The cost of LDL-A restricts its use to potentially lethal disorders, such as FH, especially for patients who are HMZ, where there is evidence of benefit over conventional therapy [32]. Cholesterol reduction was reported to be particularly cost-effective when treating patients who are at high coronary risk such as HTZ FH patients resistant to standard treatment [33].

LDL-A IN CANADA

As there is only one LDL-A program in Canada, and it is in the province of Quebec, Dr. Jacques Genest, Faculty of Medicine, McGill University, Montreal, and Dr. Claude Gagné, Lipid Research Centre, Laval University and Centre Hospitalier Universitaire de Quebéc (CHUQ) were contacted to provide some information on the treatment of patients with FH. The only place currently providing treatment with the HELP system in Canada is at the Centre Hospitalier de l'Universite Laval (CHUL) where the program has been operating since February 2001. Since the program began, until January 31, 2004, a total of 436 procedures have been performed and 11 patients with HMZ FH are treated biweekly. The LDL-A program is currently limited to patients with HMZ FH. Dr. Gagné predicts that patients with severe HTZ FH and patients who suffered sudden vascular deafness may be treated in the future with LDL-A. With the development of new pharmacological products, however, he feels that LDL-A may become obsolete. The HELP system was chosen because of its efficacy, reliability, tolerability and costs.

Dr. Genest considered that the prevalence of FH in Canada is 1:500 for HTZ and of 1:1 million for HMZ FH. He estimated that the prevalence of HMZ FH is two to three cases for the province of Alberta while the prevalence of FH is much higher in the province of Quebéc (approximately 30,000 cases of HTZ FH, with 12 to 20 cases of HMZ).

Some patients with HMZ FH responded well to a combination treatment with statin and ezetimibe but the majority of HMZ patients also require extracorporeal LDL removal. In addition, other types of patients may benefit from such a program, including patients with very high Lp(a) and vascular disease. A careful cost analysis, however, should be performed keeping in mind that LDL-A can be applied to a much larger population than only to patients with HMZ FH. From an ethical but not financial perspective, LDL-A should be available to HTZ FH patients who are refractory to drug therapy.

Until 15 years ago, there were no HMZ FH survivors past the age of 30 in Quebéc. Now, the life expectancy and the quality of life (freedom from major cardiovascular events) are greatly increased with the advent of LDL-A. Dr. Genest considers that LDL-A is the only option available in the foreseeable future for the treatment of HMZ FH patients. Liver transplantation is rarely performed for this condition, unless a heart transplant is also required. Gene therapy was attempted 10 years ago and has proven to be of little help.

Given the much higher prevalence of HTZ FH and the cost per patient per year ($40,000 CAN), a LDL extracorporeal removal program must have rigorous entry criteria.

A national registry under the auspices of the Canadian Institutes of Health Research or the Heart and Stroke Foundation of Canada or the Canadian Apheresis Study Group would be helpful to further research for this treatment approach.

DISCUSSION AND IMPLEMENTATION ISSUES

Information obtained from studies [26, 27, 33-37, 39] included in this report must be considered with care and generalization of these results may be challenging as none of these studies were conducted in Canada and most of the studies used the DSC system. They were published mainly by researchers in Japan and Germany, the countries where the LDL-A systems were developed. These studies were characterized by variability in such methodological details as:

- the number of patients in the study;
- characteristics of the patients (age, associated co-morbidity, risk factors);
- baseline concentration (%) of blood lipids and lipoproteins in the comparison groups;
- type and combination of drugs and dosages;
- pre-treatments before initiating the study;
- initiating drug treatments during different time periods while the study was ongoing;
- pre- and post-measurements of lipid profiles;
- periods of follow-up; and
- intervals between apheresis treatments.

Two studies [26, 34] included a higher proportion of patients with severe FH in the LDL-A groups due to the absence of random allocation. If patients have higher baseline levels of lipids and lipoproteins, there will likely be a greater change in the lipid and lipoprotein levels after LDL-A treatment than for those patients with lower levels at baseline. Patients with a higher level of disease severity will potentially show a greater, change in the mean per cent reduction of lipids and lipoproteins than those patients with a lesser degree of severity.

Based on the evidence from six controlled studies, the DSC Liposorber system in combination with lipid lowering drug therapy showed some promising results in lowering LDL-C levels in patients, over the age of 50 years, with severe FH treated at least once every two weeks over a one year period at minimum. The reported mean per cent decrease in LDL-C levels ranged from 34% [34] to 81% [37]. This later study [37] included patients with HMZ FH and is the reported per cent decrease for this group of patients. The drug therapy in conjunction with LDL-C differed considerably among the studies and due to this type of heterogeneity the studies' results could not be compared. These results should be interpreted very cautiously as these studies had several methodological flaws as mentioned previously.

The most commonly reported adverse effects associated with DSC and HELP therapies were hypotension, nausea and vomiting. All of the reported adverse effects were transient. The time of the treatment session for the HELP system is less then the treatment session for DSC Liposorber LA-15. However, this may be related to the fact that a higher quantity of plasma (approximately 4,500-5,500 ml) can be filtered by the Liposorber LA-15 system versus the 3,000 ml which is filtered by the HELP system. The HELP system can be used for patients on ACE-inhibitors but DSC Liposorber LA-15 system requires an interruption of this medication (if the patient is on this drug) at least 72 hours priori to each treatment.

It has been suggested that LDL-A treatment should be commenced as early as possible in children with FH before the child has any signs of coronary heart disease and/or symptoms of aortic valve disease [1, 6, 17, 23, 26, 29, 34, 35, 37, 39]. The safety and efficacy of LDL-A has not yet been established by well designed studies for pregnant women or for women during the lactation period. There is even less information available regarding the treatment for children [23].

The two studies comparing the various LDL-A systems concluded that all systems (Immunoadsorption, Liposorber, HELP, Lipidifiltration) comparatively decreased the levels of LDL-C and Lp(a).

In Canada two devices (the Liposorber LA-15 system and the HELP system) have received approval by the Medical Device Bureau, Health Canada. To date the only LDL-A program in Canada is in the province of Quebec where they use the HELP system. The program has been in operation for two years.

The decision to approve and include LDL-A in the package of services comes with difficult economical and ethical considerations. The implementation of LDL-A therapy involves a significant cost to the health care system and significant time commitment by the patients. Usually this treatment must be individualized and repeated at intervals of one to two weeks for the entire life of the patient. The decision and planning processes will need to balance costs and access on the one hand and the gravity of the disease, quality of life and the poor life expectancy of HMZ or severely ill patients with FH on the other hand.

Unfortunately, LDL apheresis, while being more specific, is more expensive than plasmapheresis. However, excellent results have been attained with plasmapheresis, especially with the addition of high dose statins and ezetimibe (personal communications, Dr. McCrindle and Dr. Frohlich).

The most commonly quoted prevalence rate of FH in the general population is one per one million individuals with HMZ FH and one per 500 individuals with HTZ FH [2, 10, 54]. Theoretically, all HMZ patients and approximately 5% to 10% of the HTZ patients could be treated by LDL-A [2]. As Alberta has a total population of 3,153,700, the estimated number of HMZ patients would be three. The number of HTZ patients who are no longer responding appropriately to standard treatment may be lower than 300 patients in view of the various combinations of newer lipid-lowering therapies, including ezetimibe. One does have to keep in mind that prevalence rates vary with ethnicity and so these would only be best estimates. Also, in the last few years a significant amount of improvements in the treatment for hyperlipidemia have been achieved and the management of this condition continues to evolve.

CONCLUSIONS

Over the last 5 years there were no systematic reviews or RCTs published which is considered the best level of research evidence. The results reported in the controlled studies which had methodological weaknesses suggest that aggressive cholesterol-lowering therapy, defined as LDL-A combined with drugs, was an effective and safe treatment for HMZ FH patients and severely ill HTZ FH patients with CAD.

LDL-A is considered a useful therapy in a very limited group of patients who have an extremely high risk for premature coronary atherosclerosis due to high levels of LDL-C. This treatment is indicated in FH especially HMZ patients, where it seems to be the treatment of choice.

Clearly further well designed research studies are required. Treatment plans for patients with FH continue to evolve. Multicentre, long term controlled studies comparing patients with FH on standard drug therapy to those treated either with LDL-A or plasmapharesis, plus standard care are necessary. Standard therapy needs to be defined consistently by the clinical experts, as well as what is considered to be a clinically relevant reduction in cholesterol and lipids. It is not clear what is the level of reduction that must be achieved by the addition of LDL-A or plasmapheresis to drug therapy in order to show a clinical benefit. More studies are needed to evaluate the effectiveness and safety of LDL-A in special categories of patients such as pregnant women, women during the lactation period and children. It may be considered unethical to treat only a portion of the patients who seem to require LDL-A and others with medication only. Randomized cross over studies may be the most appropriate design.

In addition there is a need for conducting economic analyses – cost benefit and cost effectiveness analysis to compare costs and consequences of the utilization of LDL-A with other alternative treatments available such as drug therapy or plasmapheresis or other LDL-A systems. Using valid quality of life measures are essential.

The establishment of a national registry for patients with FH and severe hyperlipidemia would be useful. This would allow for the tracking of reliable clinical outcomes for the various treatment options and would assist in addressing long term treatment issues and may result in providing effective and efficient care for this group of severely ill patients.

APPENDICES

APPENDIX A: METHODOLOGY APPROACH

Literature searches were conducted in September - October 2003, and updated in March 2004. The searches included biomedical literature databases and searches of Internet web sites for clinical trials, guidelines, research studies in progress and other assessments of low density lipoprotein apheresis for the treatment of familial hypercholesterolemia refractory to conventional treatment with diet and drug therapy.

Database	Search terms
The Cochrane Library (Issue 1, 2004) http://www.update-software.com/clibng/cliblogon.htm	(apheresis or Liposorber or plasmapheresis or aphereses or phereses or pheresis or Kaneka) and (hypercholesterolemia or hyperlipidemia)
PubMed http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed	apheresis OR Liposorber OR related articles for PMID 12887719 OR Kaneka OR related articles for PMID 12680317 OR "LDL Adsorption Column" OR "low density lipoprotein apheresis" OR "LDL apheresis" OR "Low density lipoprotein adsorption column" OR aphereses OR plasmapheresis OR phereses OR pheresis OR blood component removal OR ((HELP OR "H.E.L.P." OR "heparin-induced extra-corporeal" OR "heparin-induced extracorporeal) AND (Braun OR LDL OR apheresis)) AND hypercholesterolemia OR hyperlipidemia OR hypercholesterolemia, familial OR "high cholesterol"
EBM Reviews – ACP Journal Club (Ovid) (1991-Nov/Dec 2003)	(apheresis or Liposorber or Kaneka or aphereses or plasmapheresis).mp. [mp=title, abstract, full text, keywords, caption text]
EMBASE (Ovid) (1996-Week 10 2004) and HealthSTAR (Ovid Healthstar) (1987 to February 2004; *date limited to 1996-2004)	apheresis/ or aphereses.mp. or Liposorber.mp. or Kaneka.mp. or plasmapheresis.mp. or exp plasmapheresis/ or phereses.mp. or pheresis.mp. or blood component removal.mp. or LDL adsorption column.mp. or low density lipoprotein apheresis.mp. or LDL apheresis.mp. or low density lipoprotein adsorption column.mp. AND low density lipoprotein.mp. or exp low density lipoprotein/ or familial hypercholesterolemia.mp. or exp familial hypercholesterolemia.mp. OR hyperlipidemia.mp. or exp hyperlipidemia/ or low density lipoprotein cholesterol.mp. or exp low density lipoprotein cholesterol
CINAHL (Ovid) (1982 – March Week 1 2004; *date limited to 1998-2004)	apheresis.mp. or exp blood component removal/ or Liposorber.mp. or Kaneka.mp. OR LDL adsorption.mp. or plasmapheresis.mp. or exp plasmapheresis/ AND cholesterol.mp. or exp lipoproteins, LDL cholesterol/ or exp cholesterol/ or exp lipoproteins, HDL cholesterol/

Database	Search terms
Web of Science (Science Citation Index & Social Science Citation Index – Expanded) (*date limited to 1998-2004)	(apheresis OR Liposorber OR plasmapheresis OR aphereses OR phereses OR pheresis) AND (hypercholesterolemia OR hyperlipidemia) *limited to title words
NLM Gateway http://gateway.nlm.nih.gov/gw/Cmd	(apheresis OR pheresis OR plasmapheresis OR Liposorber) AND (hypercholesterolemia OR hypercholesterolaemia OR hyperlipidemia OR hyperlipidaemia)
CRD databases (NHS EED, DARE & HTA) http://agatha.york.ac.uk/welcome.htm	Liposorber OR apheresis OR Kaneka OR plasmapheresis OR phereses OR pheresis OR blood-component-removal AND hypercholesterolemia OR hyperlipidemia OR "low density lipoprotein" OR LDL
ECRI http://www.ecri.org	apheresis or plasmapheresis or Liposorber
NEOS Library Consortium Catalogue http://www.library.ualberta.ca/catalogue/	apheresis or plasmapheresis or blood component removal
Cabot http://www.mycabot.ca	apheresis or plasmapheresis
National Research Register (Issue 1 2004) http://www.update-software.com/nrr/CLIBINET.EXE?A=1&U=1001&P=10001	apheresis or plasmapheresis or Liposorber
CMA INFOBASE Clinical Practice Guidelines http://mdm.ca/cpgsnew/cpgs/index.asp	apheresis or plasmapheresis or hypercholesterolemia
National Guideline Clearinghouse http://www.guideline.gov	apheresis or plasmapheresis or hypercholesterolemia
New Zealand Guidelines Group http://www.nzgg.org.nz/	apheresis or plasmapheresis or hypercholesterolemia
ClinicalTrials.gov http://www.clinicaltrials.gov	apheresis or plasmapheresis or hypercholesterolemia
Current Controlled Trials http://controlled-trials.com/	apheresis or plasmapheresis
CenterWatch Clinical Trials Listing Service http://www.centerwatch.com	apheresis or plasmapheresis

In addition, the web sites of Canadian and international health technology assessment and evidence-based medicine sites were scanned or searched; a limited Internet search was run using Google.com and the phrase "LDL apheresis", and Health Canada was contacted for information on the regulatory status of these devices in Canada.

Literature searches were conducted by Ms. Leigh-Ann Topfer, Canadian Coordinating Office for Health Technology Assessment, Edmonton, Alberta

Selection of studies

A literature search of articles which reported on the use of the DSC and the HELP LDL-A systems for the treatment of patients with FH were conducted.

The studies identified by the search strategy were retrieved, reviewed and assessed to determine the relevance of each study. Inclusion criteria for selection of studies for LDL-A based on the best level of available evidence were:

- Device: DSC system (Liposorber), and HELP system;
- Indication: familial hypercholesterolemia (HMZ and HTZ);
- Target population: all ages (adults & children);
- Intervention: low density lipoprotein removal;
- Publication limits: starting with 1998 (note: one old RCTs from 1995 was included because of its relevance);
- Language: English;
- Abstract of the study available.

The exclusion criteria for selection of studies were:

- Other devices than the DSC system (Liposorber) and the HELP system;
- Case reports and case series that present DSC system (Liposorber) or the HELP system;
- Presentation of combined results regarding: different apheresis systems and/or HTZ and HMZ patients;
- Absence of specification regarding the FH population included (if FH patients were HTZ and/or HMZ);
- Language: other than English;
- Abstract of the study unavailable;
- In vitro studies.

We selected the best study designs available which were controlled studies that compared the efficacy and safety of LDL apheresis using the DSC system and/or the HELP system with conventional drug therapy for lowering cholesterol level (six controlled studies) and studies that compared the DSC system and/or the HELP system with other apheresis system(s) (two studies).

For some of the selected studies the outcome measures had to be calculated from the data provided in order to present the same information for all studies. The acute lowering of lipoproteins (the mean % decrease) for each of the plasma components was calculated by difference in pre- and post- procedure lipid values (means) as per cent of the initial value. The mean % decrease = [pre-apheresis (mean) value minus post-apheresis (mean) value] X 100/pre-apheresis (mean) value

The studies excluded based on the exclusion criteria are listed in Table 10 (see Table 10, Appendix F).

APPENDIX B: DETAILED DESCRIPTION OF LDL-A SYSTEMS

The **dextran sulfate cellulose (DSC)** system is manufactured by Kaneka Corporation, Osaka, Japan and distributed by Kaneka Pharma America Corporation, New York. The dextran sulfate has a structure similar to that of the LDL receptor in the human body and seems to act as a type of pseudo receptor for LDL. This product is an integrated automated extracorporeal blood processing system consisting of a control/monitor machine and three disposables (an adsorption column comprised of two columns, each containing 150 ml of dextran sulfate-cellulose adsorbent (Liposorber LA-15), a plasma separator and the tubing system for plasmapheresis) (available: http://www.liposorber.com).

During LDL apheresis, blood is withdrawn from the patient's arm through a plastic tube and flows through a hollow-fiber plasma separator that separates plasma from whole blood. The plasma flows through the column which removes the LDL cholesterol. The LDL depleted plasma ("cleaned" plasma) is then recombined with the cellular components and returned to the patient. When the column becomes saturated, the flow of plasma is switched to a second dextran sulfate column (Liposorber LA-15), while the first is reactivated by flushing out the adsorbed LDL-C.

After the completion of the procedure, the components of the instrument that have been in contact with the patient's blood, including the tubing and columns are discarded. A total of four to five liters of plasma can be treated and the process takes approximately 3 hours. The system can also operate with only one column with a higher capacity (Liposorber LA-40) but requires different equipment for plasma separation (manufactured by COBE Spectra centrifugation machine) [2, 3, 7, 14, 20, 21, 25, 32, 55, 56] (personal communication, Kaneka Pharma America Co., New York).

The **heparin induced LDL precipitation (H.E.L.P.)** system is manufactured by B. Braun Melsungen, Germany. This system is similar to other LDL apheresis procedures but uses a natural anticoagulant – heparin as the medium for precipitation of the lipoproteins. The heparin interacts with LDL molecules and forms LDL heparin precipitate complexes which are then separated from the plasma and retained in a specifically designed polycarbonate membrane filter.

Blood is withdrawn from the patient via venous access into an extracorporeal circle. The plasma and blood cells are separated by a plasma filter. The plasma is continuously mixed with a sodium acetate buffer pH 4.85 and heparin (100,000 U/L). Before returning the plasma to the patient, the excess heparin is adsorbed and the pH is normalized (increased back to 7.4) by a dialysis procedure. The plasma is then reunited with the blood cells and transferred back to the patient via the cubital vein in the other arm. Anticoagulation with heparin (2,200 U/L) is stopped 30 minutes before the end of the treatment.

All disposables are single-use sterile components. Within a two hour session, three liters of plasma is filtrated on average. The standard HELP therapy requires a dialysis module which needs an external reverse osmosis device for the online production of dialysis fluid. In order to create a more friendly HELP procedure a new system the Plasmat Futura system that works without reverse osmosis was developed and is in the final stages of approval. Some promising results with this new device are presented in the published literature. This new system delivers dialysate in sterile bags and is independent of a proper dialysis unit. The performance of the new system is comparable with the standard HELP-Plasmat machine [2, 3, 7, 20, 21, 32, 41, 48, 57, 58] (available on CD, B. Braun Inc.).

The **Immunadsorption system** manufactured by the TPS Baxter, Deerfield Illinois US is a system which selectively removes LDL from plasma using anti-LDL antibodies. The system consists of a continuous flow cell separator containing polyclonal or monoclonal sheep (goat) antibodies to human apolipoprotein B100. The plasma is separated from blood cells and is passed through one of the two immunoadsorption columns. Before the first column is saturated with adsorbed lipoproteins, the plasma flow is switched to the other column. The off-line column is regenerated. The treated plasma is then mixed with the cellular components of the blood and returned to the patient. Anticoagulation is achieved with heparin and acid citrate dextrose (ACD). The entire procedure takes 3 to 4 hours and is monitored by a computer. After the treatment, the columns are rinsed and stored in sodium azide between treatments. Each patient has two columns that are reused during each treatment. The columns last for an average of 50 treatments (approximately one year) [3, 7, 32, 41, 51].

The **DALI system** (Direct Adsorption of Lipoproteins Hemoperfusion), manufactured by Fresenius, St. Wendel, Germany, selectively removes lipoproteins from the whole-blood without preliminary separation of plasma from blood cells. The system can run at different adsorber sizes: DALI 500, 750, 1000 ml and the adsorber (column) contains polyacrylate-coated polyacrylamide beads that electrochemically interact with lipoproteins and eliminate them. Besides lipoproteins, the system also adsorbs calcium and magnesium ions from the blood. Therefore the columns have to be pre-rinsed with a solution containing these electrolytes. After passing the adsorber, the blood depleted of its lipoproteins is returned to the patient. Anticoagulation is initiated by heparin and maintained by ACD. The column is used for only one treatment [2, 3, 7, 20, 32, 51].

APPENDIX C: TECHNICAL FEATURES: THE DSC SYSTEM AND THE HELP SYSTEM

Table 5: Technical features regarding the Liposorber LA-15 System and the HELP System

	Liposorber LA-15	HELP
Procedural steps	Plasma perfusion using dextran sulfate-cellulose which adsorbs LDL, VLDL and Lp(a). Alternative use of two adsorption columns (Liposorber LA-15) through regeneration. Combine LDL-depleted plasma with blood cell components and return to the patient.	Precipitation of LDL, VLDL and Lp(a) from plasma using a heparin complex in an acidic solution (pH=5.12). Filtration of LDL, VLDL and Lp(a) heparin complex. Pass plasma through a heparin adsorber. Raise the pH of plasma to physiological level and start ultrafiltration through bicarbonate dialysis. Combine LDL-depleted plasma with blood cell components and return to the patient.
Treatable plasma volume	Approximately 10,000 ml The apheresis machine (MA-01) is programmed to process up to 9,950ml of plasma in one run. Usually approximately 4,500-5,500 ml is processed during a treatment session.	3,000 ml
Extracorporeal volume	400ml (170ml as whole blood and 230ml as plasma)	400-550 ml (100-150 ml as whole blood and 300-400 as plasma)
Anticoagulation	Heparin	Heparin
Set-up time/procedure (min. aprox.)	45-90 (may vary depending on experience of an operator)	60
Time per session (hours)	2.5-3.0 (Time varies depending on how much plasma volume is to be processed and the patient's blood flow rate).	1.0-2.0
Concomitant ACE-inhibitors treatment	No, as the patient needs to interrupt this therapy for at least 72 hours prior to apheresis.	Yes

continued on next page

Table 5: Technical features regarding the Liposorber LA-15 System and the HELP System (cont'd)

	Liposorber LA-15	HELP
Applicability for all ages (children & adults)	Yes In the US, the manufacturer doesn't recommend the treatment of patients weighing less than 15kgs or younger than 5 years old. However, the system is applied to smaller patients if they can tolerate the procedure.	Yes The recommended weight limit for patients is 37 kgs
Training required (number of hours)	Standard training is provided by a nurse and consists of a 3 days course on site including an actual treatment of a patient on the third day. Upon necessity, this will be repeated on the second treatment (usually 2 weeks later). A dedicated clinical staff member is available by hot-line to answer any questions or concerns.	3-5 days
Downtime maintenance time per year	A preventive maintenance is set once per year and ensures that the machine will be durable for more than ten years under normal usage.	Minimal (does not interfere with therapy schedule)

Information was obtained from literature and from Kaneka Pharma America Co., New York (Liposorber LA-15) and B. Braun Medical Inc. (HELP)

APPENDIX D: DETAILS ON STUDIES OF EFFICACY/EFFECTIVENESS

Table 6: Controlled studies using DSC*

<table>
<tr><th>Author, Year of publication
Country
Study design</th><th>Sample size and characteristics
Procedure(s) ± drug therapy</th><th>Apheresis: Nr. / patient, Follow-up period (mean treatment period)
Treatment interval</th><th>Mean decrease (acute lowering) (%)
Conclusions</th></tr>
<tr><td>Matsuzaki et al., 2002 [34]
Japan
Prospective multicenter controlled study (8 centers)
Note: Patients which severe FH or progressed coronary artery disease (CAD) tended to be assigned to the LDL-A group</td><td>N=18
n_1=7 patients(HTZ)- cholesterol-lowering drug therapy: HMG-CoA reductase inhibitors (pravastatin or simvastatin)
Distribution by gender:
5 males, 2 females
Distribution by age:
Mean 54 ± 15 years
n_2=11 patients (HTZ) - LDL-A (Liposorber) and cholesterol-lowering drug therapy: HMG-CoA reductase inhibitors (pravastatin or simvastatin)
Distribution by gender:
8 males, 3 females
Distribution by age:
Mean 50 ± 13 years</td><td>Nr. of apheresis/patient:
not specified
Follow-up period:
1 year
Treatment interval:
biweekly</td><td>Mean decrease (%):
<table>
<tr><th>Lipids</th><th>Control (n_1=7)</th><th>Apheresis (n_2=11)</th></tr>
<tr><td>TC</td><td>-1.2</td><td>28.4</td></tr>
<tr><td>TG</td><td>9.8</td><td>2.8</td></tr>
<tr><td>LDL-C</td><td>-4</td><td>34.3</td></tr>
<tr><td>HDL-C**</td><td>-2.3</td><td>-9.1</td></tr>
</table>
Note: the mean decrease of lipids was measured after one year of treatment from baseline and follow-up values.
Patients were already on HMG-CoA reductase inhibitor when baseline lipid values were measured. That may be the reason for small changes of the levels of lipids in the medication group.
Conclusion:
A statistical significant regression of coronary artery lesions was observed in FH patients with advanced CAD treated with LDL-apheresis and lipid lowering drugs compared with patients who received only drug therapy.
The results suggested that the combination therapy may induce regression of coronary atherosclerotic plaque in FH patients.</td></tr>
</table>

* There are two devices available, Liposorber LA-15 and Liposorber LA-40. Some studies identify that LA-15 was used; in other studies the information is not available.

**How the change in HDL-C was measured did not seem to be consistent among the studies.

continued on next page

Table 6: Controlled studies using DSC* (cont'd)

<table>
<tr><th>Author, Year of publication Country
Study design</th><th>Sample size and characteristics
Procedure(s) ± drug therapy</th><th>Apheresis: Nr. / patient, Follow-up period (mean treatment period)
Treatment interval</th><th>Mean decrease (acute lowering) (%)
Conclusions</th></tr>
<tr><td>Nishimura et al., 1999 [35]
Japan
Prospective multicenter nonrandomized controlled study (12 centers)
Phases of the study:
I. short trial (two times of biweekly LDL-A)
II. distribution of patients in two groups (n_1 & n_2)
Note: This study is known as
L-CAPS Study</td><td>N=36
n_1=11 patients(HTZ)- cholesterol-lowering drug therapy: (pravastatin 10pt; probucol 10pt; cholestyramine 8pt)
Distribution by gender:
8 males, 3 females
Distribution by age:
Mean 51± 8 years
n_2=25 patients (HTZ) - LDL-A (Liposorber) and cholesterol-lowering drug therapy: (pravastatin 24 patients (pt); probucol 24pt; cholestyramine 20pt)
Distribution by gender:
17 males, 8 females
Distribution by age:
Mean 51 ± 10 years</td><td>Nr. of apheresis/patient:
mean 50.7 (1268 apheresis)
Follow-up period:
2.3 years (28 months)
Treatment interval:
17 days</td><td>Mean decrease (%):
<table>
<tr><th>Lipids</th><th>Control
(n_1=11)</th><th>Apheresis
(n_2=25)</th></tr>
<tr><td>TC</td><td>29.6</td><td>35.7</td></tr>
<tr><td>TG</td><td>19.6</td><td>19.8</td></tr>
<tr><td>LDL-C</td><td>34.1</td><td>43.1</td></tr>
<tr><td>HDL-C**</td><td>10.5</td><td>-6.9</td></tr>
</table>
Note: The mean decrease of lipids for the group of patients on apheresis was calculated using baseline and average mean values.
The differences in lipids were stable throughout the treatment period.
In the control group, follow-up measurements of lipids were done every 3 months throughout the study. The mean decrease in the control group was calculated from baseline and follow-up data.
Conclusion:
Intensive cholesterol lowering therapy with LDL-A associated with lipid lowering drugs can achieve a substantial decrease in LDL-C levels to induce regression of coronary lesions in FH patients with advanced CAD.</td></tr>
</table>

* There are two devices available, Liposorber LA-15 and Liposorber LA-40. Some studies identify that LA-15 was used; in other studies the information is not available.

**How the change in HDL-C was measured did not seem to be consistent among the studies.

continued on next page

Table 6: Controlled studies using DSC* (cont'd)

<table>
<tr>
<th>Author, Year of publication
Country
Study design</th>
<th>Sample size and characteristics
Procedure(s) ± drug therapy</th>
<th>Apheresis: Nr. / patient, Follow-up period (mean treatment period)
Treatment interval</th>
<th>Mean decrease (acute lowering) (%)
Conclusions</th>
</tr>
<tr>
<td>Mabuchi et al., 1998 [26]
Japan
Multicentre controlled study
Note: More patients with severe FH were enrolled in the LDL -A group.
The study is known as: Hokuriku FH LDL-A Study</td>
<td>N=130 patients with coronary stenosis (>75%)
n_1=87 patients (HTZ) - cholesterol-lowering drug therapy: (statin 67pt; probucol 54pt; cholestyramine 19pt; fibrate 7pt)
Distribution by gender:
65 males, 22 females
Distribution by age:
Mean 59± 12 years
n_2=43 patients (HTZ) - LDL-A (Liposorber) and cholesterol-lowering drug therapy: (statin 37patients (pt); probucol 25pt; cholestyramine 11pt; fibrate 2pt)
Distribution by gender:
32 males, 11 females
Distribution by age:
Mean 57 ± 10 years</td>
<td>Nr. of apheresis/patient:
not specified
Follow-up period:
6 years
<i>Average treatment periods:</i>
5.9 ± 3.4 years LDL-A
6.1 ± 3.0 years drug treatment
Treatment interval:
two weeks</td>
<td>Mean decrease (%):
<table>
<tr><th>Lipids</th><th>Control (n_1=87)</th><th>Apheresis (n_2=43)</th></tr>
<tr><td>TC</td><td>25</td><td>53</td></tr>
<tr><td>TG</td><td>22</td><td>53</td></tr>
<tr><td>LDL-C</td><td>28</td><td>58</td></tr>
<tr><td>HDL-C**</td><td>12</td><td>22</td></tr>
</table>
Note: Time of measurement of the mean decrease of lipids was not specified
Conclusion:
After 6 years of follow-up, the rate of total coronary events was 72% lower in the LDL-A than in the drug therapy group.
LDL-A is effective as a treatment of coronary heart disease in FH HTZ, and may become the therapy of choice in severe types of FH.</td>
</tr>
</table>

* There are two devices available, Liposorber LA-15 and Liposorber LA-40. Some studies identify that LA-15 was used; in other studies the information is not available.

**How the change in HDL-C was measured did not seem to be consistent among the studies.

continued on next page

Table 6: Controlled studies using DSC* (cont'd)

<table>
<tr>
<th>Author, Year of publication Country
Study design</th>
<th>Sample size and characteristics
Procedure(s) ± drug therapy</th>
<th>Apheresis: Nr. / patient, Follow-up period (mean treatment period)
Treatment interval</th>
<th>Mean decrease (acute lowering) (%)
Conclusions</th>
</tr>
<tr>
<td>Koga et al., 1999 [36]
Japan
Controlled study</td>
<td>N=21
n_1=10 patients (HTZ) (control group) - cholesterol-lowering drug therapy (pravastatin 8pt; probucol 7 pt)
Distribution by gender:
4 males, 6 females
Distribution by age:
Mean 63± 10 (range 44-74) years
n_2=11patients (2HMZ and 9 HTZ)- LDL-A (Liposorber) and cholesterol-lowering drug therapy: (pravastatin 11pt; probucol 10 pt)
Distribution by gender:
7 males, 4 females
Distribution by age:
Mean 41± 2.2 (range 34-56) years</td>
<td>Nr. of apheresis patient:
not specified
Follow-up period:
(mean treatment period)
7.8 ± 2.2 years (range 5-11)
Treatment interval:
two weeks in HMZ
every 2-4 weeks in HTZ</td>
<td>Mean decrease (%):
<table>
<tr><th>Lipids</th><th>Control</th><th colspan="2">Apheresis</th></tr>
<tr><th></th><th>HTZ</th><th>HMZ</th><th>HTZ</th></tr>
<tr><td>TC</td><td>21.7</td><td>56.4</td><td>56.5</td></tr>
<tr><td>TG</td><td>41.9</td><td>19.5</td><td>17.5</td></tr>
<tr><td>LDL-C</td><td>22.9</td><td>60.5</td><td>56.8</td></tr>
<tr><td>HDL-C**</td><td>4.6</td><td>45.5</td><td>4.0</td></tr>
</table>
Note: The TC and LDL-C levels at baseline in the LDL-A group were significantly higher than those in the medication (control) group.
The moment of measurement of the mean decrease during the follow-up period was not clearly specified (pre – immediately before treatment; post – immediately after the treatment).
Conclusion:
No substantial difference was observed between severe FH patients from the group treated with apheresis and drugs and the mild FH patients treated with drugs in the progression of existing plaques and the formation of new plaque in the carotid artery.
However, the annual progression rate of mean maximum intima-media thickness in the common carotid artery was significantly lower in the group treated with LDL-A, suggesting regression. The long-term treatment with combined LDL-A and drugs may delay the progression of the atherosclerotic process and prompt the stabilization of atheromatous plaque in severe FH patients.</td>
</tr>
</table>

* There are two devices available, Liposorber LA-15 and Liposorber LA-40. Some studies identify that LA-15 was used; in other studies the information is not available.

**How the change in HDL-C was measured did not seem to be consistent among the studies.

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Table 6: Controlled studies using DSC* (cont'd)

<table>
<tr><th>Author, Year of publication Country
Study design</th><th>Sample size and characteristics
Procedure(s) ± drug therapy</th><th>Apheresis: Nr. / patient, Follow-up period (mean treatment period)
Treatment interval</th><th>Mean decrease (acute lowering) (%)
Conclusions</th></tr>
<tr>
<td>Gordon et al., 1998 [37]
United States
Multicenter study (9 centers):
I. controlled treatment phase (N=64; only 54 completed, 19 HTZ discontinued) all HMZ received LDL-A; HTZ were randomly assigned to LDL-A and drug therapy or only drugs (4:1 ratio)
II. optional phase
(N=49; at 5 years there were 29 patients and 20 discontinued)
Note: The study was sponsored by a grant from the Kaneka Pharma America Co. New York.</td>
<td>N=?
Distribution by gender:
Not specified
Distribution by age:
Between 5 and 70 years
Controlled treatment phase:
N=64
n_1=9 HTZ - cholesterol-lowering drug therapy (control group)
n_2=10 HMZ - LDL-A and drugs?
n_3=45 HTZ - LDL-A and cholesterol-lowering drug therapy (drugs not specified)

Optional phase:
N=49
n_2=10 HMZ - LDL-A and drugs?
n_3=39 HTZ - LDL-A and cholesterol-lowering drug therapy (drugs not specified)</td>
<td>Nr. of apheresis/patient:
controlled phase: 588 (total)
follow-up phase: 3,314 (total)
Controlled treatment phase:
5 years
first phase: 18 weeks LDL-A + 4 weeks observation without LDL-A
optional phase: not specified
Treatment interval:
I. contolled treatment phase: once every two weeks for 6 weeks, than change the frequency of treatment based upon cholesterol level (12 weeks), than discontinued and the rebound in TC and LDL-C was observed over the following 4 weeks
II. optional phase:
treatment every 11± 5 days HMZ
treatment every 14± 6 days HTZ</td>
<td>Mean decrease (%):
<table>
<tr><th>Lipids</th><th colspan="3">Controlled treatment phase</th><th colspan="2">Optional phase</th></tr>
<tr><th></th><th>Control HTZ (n_1=9)</th><th>HMZ (n_2=10)</th><th>HTZ (n_3=45)</th><th>HMZ (n_2=10)</th><th>HTZ (n_3=39)</th></tr>
<tr><td>TC</td><td>?</td><td>70± 4</td><td>61± 2</td><td>66± 2</td><td>61± 2</td></tr>
<tr><td>TG</td><td>?</td><td>59± 9</td><td>60± 9</td><td>49± 9</td><td>56± 7</td></tr>
<tr><td>LDL-C</td><td>?</td><td>81± 5</td><td>76± 2</td><td>76± 2</td><td>76± 4</td></tr>
<tr><td>HDL-C**</td><td>?</td><td>13± 5</td><td>5± 4</td><td>14± 3</td><td>9± 3</td></tr>
</table>
Mean decrease ± <i>SD</i>
Note: The moment of measurement of the mean decrease during the study was not clearly specified
Mean decrease % of lipids in the control group was not specified in the article
Conclusion:
Results obtained during the long-time follow-up period sustain the efficacy and safety of LDL-A in patients with HTZ and HMZ FH who are inadequately controlled with drug therapy.</td>
</tr>
</table>

* There are two devices available, Liposorber LA-15 and Liposorber LA-40. Some studies identify that LA-15 was used; in other studies the information is not available.

**How the change in HDL-C was measured did not seem to be consistent among the studies.

continued on next page

Table 6: Controlled studies using DSC* (cont'd)

<table>
<tr><th>Author, Year of publication Country
Study design</th><th>Sample size and characteristics
Procedure(s) ± drug therapy</th><th>Apheresis: Nr. / patient, Follow-up period (mean treatment period)
Treatment interval</th><th>Mean decrease (acute lowering) (%)
Conclusions</th></tr>
<tr><td>Thompson et al., 1995 [27]
United Kingdom
Controlled study Randomized trial (multicenter - 3 centres)
I. drug therapy: colestipol for 6 weeks
II. patients (46) randomly assigned to one of two groups; 7 dropped out (4 from apheresis group and 3 from control group)
Note: Kaneka (Germany) provide all the apheresis equipment and disposables used in the trial</td><td>N=39
n_1=19 patients(HTZ)- cholesterol-lowering drug therapy: (simvastatin; colestipol)
Distribution by gender:
14 males, 5 females
Distribution by age:
Mean 49.8 ± 7.4 years
n_2=20 patients (HTZ) - LDL-A (Liposorber) and cholesterol-lowering drug therapy: simvastatin
Distribution by gender:
14 males, 6 females
Distribution by age:
Mean 49.2 ± 7.8 years</td><td>Nr. of apheresis/patient:
948/20 = 47.5
Follow-up period:
2.1 years
Treatment interval:
two weeks</td><td>Mean decrease (%):
<table>
<tr><th>Lipids</th><th>Control (n_1=19)</th><th>Apheresis (n_2=20)</th></tr>
<tr><td>TC</td><td>34.6</td><td>54.1</td></tr>
<tr><td>TG</td><td>10</td><td>47.1</td></tr>
<tr><td>LDL-C</td><td>44.3</td><td>66.3</td></tr>
<tr><td>HDL-C**</td><td>-4.7</td><td>9.1</td></tr>
</table>
Note: Mean decrease was calculated based on values measured pre-apheresis and immediately after LDL-A (post-apheresis). The moment of measurement of the lipids during the follow-up period was not specified.
The percentage changes from baseline values were calculated (and than represented graphically) based on interval means between consecutive procedures.
Conclusion:
The mean % diameter stenosis of lesions was significantly greater in the LDL-A group than in the drug group at baseline (32.89% vs. 29.96%, p=0.03). After adjustment for this difference, this parameter after 2 years of treatment did not differ significantly between groups either on a per patient basis (95% CI -2.9% to 3.6%) or on a per lesion bases.
LDL-A seems to offer no advantage over combination drug therapy in drug responsive FH HTZ. However, LDL-A provides an alternative option for treating those HTZ with established coronary disease who are intolerant of, or unresponsive to, combination drug therapy.</td></tr>
</table>

* There are two devices available, Liposorber LA-15 and Liposorber LA-40. Some studies identify that LA-15 was used; in other studies the information is not available.

**How the change in HDL-C was measured did not seem to be consistent among the studies.

Table 7: Comparative study of LDL-A Systems

<table>
<tr><th>Author, Year of publication Country
Study design</th><th>Sample size and characteristics
Procedure(s) ± drug therapy</th><th>Apheresis: Nr. / patient, Follow-up period (mean treatment period)
Treatment interval</th><th>Mean decrease (acute lowering) (%)
Conclusions</th></tr>
<tr><td>Richter et al. 1999 [39]
Germany
Comparative study</td><td>N=34 (HTZ)
Distribution by gender:
21 males, 13 females
Distribution by age:
47± 9 years old
n_1 =18 Immunoadsorption
8 patients started to receive simvastatin after 3 years
n_2 = 8 Liposorber*
6 patients started to receive simvastatin after 6 months
n_3 = 8 HELP
5 patients started to receive simvastatin after 2 years</td><td>Nr. of apheresis/patient:
Immunoadsorption
3499/18=194.4
Liposorber
579/8=72.4
HELP
1497/8=187.1
Follow-up period:
4.6± 2.6 years (range 0.9-8 years)
Treatment interval:
30 patients – weekly
4 patients – two weeks</td><td>Mean decrease (%):
<table>
<tr><th>Lipids</th><th>Immunoad. (n_1=18)</th><th>Liposorber (n_2 = 8)</th><th>HELP (n_3 = 8)</th></tr>
<tr><td>TC</td><td>52.2</td><td>54.3</td><td>49.3</td></tr>
<tr><td>TG</td><td>44.4</td><td>42.8</td><td>44.4</td></tr>
<tr><td>LDL-C</td><td>61.7</td><td>65.3</td><td>58.7</td></tr>
<tr><td>HDL-C**</td><td>15.4</td><td>16.6</td><td>16.6</td></tr>
<tr><td>Lp(a)</td><td>51.4</td><td>48.6</td><td>67.7</td></tr>
</table>
Note: measurement during one LDL-A procedure (mean of last five treatments)
The long-term results of the global coronary score (for 23 patients):
4 patients – regression of coronary atherosclerosis (2 HELP; 2 Immunoadsorption) and in all other cases examined there was no change in the progression of coronary lesions.
The global change scores of the bypass vessels (11 patients):
1 occlusion and myocardial infarction after 2 years (Liposorber)
1 progression of atherosclerosis in these vessels (HELP)
Conclusion:
All three LDL-A systems were comparably effective in lowering atherogenic lipoproteins.</td></tr>
</table>

* There are two devices available, Liposorber LA-15 and Liposorber LA-40. Some studies identify that LA-15 was used; in other studies the information is not available.

**How the change in HDL-C was measured did not seem to be consistent among the studies.

continued on next page

Table 7: Comparative study of LDL-A Systems (cont'd)

<table>
<tr><th>Author, Year of publication Country
Study design</th><th>Sample size and characteristics
Procedure(s) ± drug therapy</th><th>Apheresis: Nr. / patient, Follow-up period (mean treatment period)
Treatment interval</th><th>Mean decrease (acute lowering) (%)
Conclusions</th></tr>
<tr>
<td>Julius et al., 2000 [33]
Germany
Cross-over study

Note: Patients were treated with apheresis before entry in the study for a minimum of 2 years.
Patients were under lipid lowering medication (type of drugs not specified) and the dosage remained unchanged for the entire study period.</td>
<td>Part I.
N=5 HTZ
Distribution by gender:
4 males, 1 females
Distribution by age:
Mean age: 64 years
n_1=5 HELP apheresis
n_1=5 Lipidfiltration apheresis with Cascadeflo AC-1770
Part II. (added one patient)
N=6 HTZ
Distribution by gender:
4 males, 2 females
Distribution by age:
Mean age: 61.5 years
n_2=6 HELP apheresis
n_2=6 new Lipidfiltration Lipidfilter EC-50</td>
<td>Nr. of apheresis/patient:
<i>Part I.</i>
4 / patient (two treatments on each system - 2 HELP, 2 Lipidfiltration AC-1770
<i>Part II.</i>
4 / patient (two treatments on each system - 2 HELP, 2 Lipidfiltration EC-50
Follow-up period:
Part I. - one month
Part II.- one month
Treatment interval:
weekly</td>
<td>Mean decrease (%):
<table>
<tr><th>Lipids</th><th colspan="2">Part I</th><th colspan="2">Part II</th></tr>
<tr><th></th><th>HELP
(n_1=5)</th><th>Lipidfiltration AC-1770
(n_1=5)</th><th>HELP
(n_2=6)</th><th>Lipidfiltration EC-50
(n_2=6)</th></tr>
<tr><td>TC*</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>TG</td><td>60.7</td><td>53.4</td><td>51.6</td><td>57.5</td></tr>
<tr><td>LDL-C</td><td>54.0</td><td>56.3</td><td>61.3</td><td>61.4</td></tr>
<tr><td>HDL-C**</td><td>-0.4</td><td>17.4</td><td>1.3</td><td>6.4</td></tr>
<tr><td>Fibrinogen</td><td>58.0</td><td>51</td><td>62.1</td><td>41.5</td></tr>
<tr><td>Lp(a)</td><td>61.5</td><td>52.8</td><td>56.3</td><td>60.5</td></tr>
</table>
Note: values represent means, in case of Lp(a) only 4 blood samples could be analysed.
* values on TC were not provided
Conclusion:
Results showed that the reduction rates of LDL-cholesterol, lipoprotein (a) and triglycerides were essentially identical for both methods.
Lipidfiltration and HELP both resulted in a reduction of plasma viscosity and hemorheologically relevant plasma proteins like fibrinogen.
To avoid a fibrinogen depletion in individual patients when treated with either LDL-A systems, Lipidfiltration EC-50 might be favorable due to its moderate reduction rate for fibrinogen compared to HELP.</td>
</tr>
</table>

**How the change in HDL-C was measured did not seem to be consistent among the studies.

APPENDIX E: EVIDENCE OF SAFETY AND CARDIOVASCULAR EVENTS

Table 8: Short term adverse effects due to LDL-A

Study	Results (number of patients affected)
Matsuzaki et al. [34]	The analysis of the incidence of events was not possible (due to the short period of follow-up)
Nishimura et al. [35]	The only specification in the study was: no serious adverse effects occurred during the trial
Mabuchi et al. [26]	Not specified
Koga et al. [36]	Not specified
Gordon et al. [37]	Combined (aggregate) data reported in the initial contingent of patients (N=64) LDL-A (Liposorber LA-15) **Total events: 36 patients** 23 Hypotension 14 Nausea / vomiting 9 Flushing 8 Chest pain 6 Fainting 6 Lightheadedness 6 Anemia 3 Abdominal discomfort 3 Numbness / tingling 3 Headache 2 Bradycardia 2 Shortness of breath 2 Hemolysis 2 Itching / hives 2 Bleeding/blood loss/anemia
Thompson et al. [27]	Not specified
Richter et al. [39]	N=34 (HTP): n_1 =18 Immunoadsorption, n_2 = 8 Liposorber, n_3 = 8 HELP **Combined (aggregate) data:** 28 Problems with venous access 20 Hypotension 13 Nausea 11 Angina pectoris 9 Feeling of warmth 8 Paresthesia (arms) 7 Dizziness 7 Ache (arms, hands) 5 Dyspnea 3 Cranial pressure 3 Flush 3 Headache
Julius et al. [33]	Not specified

Table 9: Long term events measured in patients treated with LDL-A

Study	Results (number of patients affected)
Matsuzaki et al. [34]	Not specified (short period of follow-up: one year)
Nishimura et al. [35]	**Cholesterol-lowering drug therapy** n_1=11 patients(HTZ): 1 bypass surgery 3 patients - hospital admission for unstable angina **LDL-A (Liposorber) and cholesterol-lowering drug therapy** n_2=25 patients (HTZ): 1 angioplasty 1 bypass surgery 1 hospital admission for unstable angina
Mabuchi et al. [26]	**Cholesterol-lowering drug therapy** n_1=87 patients (HTZ): 1 death due to myocardial infarction **LDL-A (Liposorber) and cholesterol-lowering drug therapy** n_2=43 patients (HTZ): 1 death due to myocardial infarction
Koga et al. [36]	**Cholesterol-lowering drug therapy** n_1=10 patients (HTZ): 2 PTCA (repeated twice during observation period) 2 CABG **LDL-A (Liposorber) and cholesterol-lowering drug therapy** n_2=11patients (2HMZ and 9 HTZ): 1 death 3 PTCA
Gordon et al. [37]	Not specified
Thompson et al. [27]	**Cholesterol-lowering drug therapy** n_1=19 patients(HTZ): 1 angioplasty 2 myocardial infarction 1 hepatic dysfunction after 15 months' treatment under simvastatin **LDL-A (Liposorber LA-15) and cholesterol-lowering drug therapy** n_2=20 patients (HTZ): 1 angioplasty
Richter et al. [39]	N=34 (HTZ): n_1 =18 Immunoadsorption, n_2 = 8 Liposorber, n_3 = 8 HELP **Combined (aggregate) data:** 3 deaths – very severe coronary lesions (due to coronary heart disease) 1 non-fatal myocardial infarction
Julius et al. [33]	Not specified

APPENDIX F: EXCLUDED STUDIES

Table 10: Excluded studies

Author	Type of study	Comments (reasons for exclusion)
Bambauer et al. [59]	Comparative study, four apheresis systems: DSC, DALI, Therasorb and Lipopak (Immunoadsorption)	Presented combined results on HTZ and HMZ
Bambauer et al. [60]	Comparative study, four apheresis systems: DSC, DALI, Therasorb and Lipopak (Immunoadsorption)	Presented combined results on HTZ and HMZ
Parhofer et al. [61]	Comparative study, four apheresis systems: HELP, Immunoadsorption, DSC, Cascade-filtration.	Not all the patients included were FH patients (information received from the principal author)
Schmaldienst et al. [62]	Cross-over study with three apheresis systems (DSC, Therasorb - Immunoadsorption, DALI)	Reported combined data on HTZ and HMZ patients
Bambauer [63]	Comparative study, four different apheresis systems: DSC, DALI, Therasorb and Lipopak (Immunoadsorption)	Presented combined results on HTZ and HMZ
Empen et al. [64]	Comparative study, applied three apheresis systems: DALI, DSC, HELP	Not all the patients included were FH patients (information received from the principal author)
Bambauer et al. [65]	Comparative study, four apheresis systems: Liposorber, DALI, Therasorb and Lipopak (Immunoadsorption)	Presented the results combined for all apheresis systems included and for HTZ and HMZ patients
Aengevaeren et al. [66]	Controlled study (apheresis + drug therapy versus only drug therapy)	Included patients with FH and primary hypercholesterolemia. The study mainly evaluated the effect on improvements of regional myocardial perfusion.
Richter et al. [67]	Comparative study, three apheresis systems: Immunoadsorption, DSC, HELP	Published the same article (results) in another journal. That study [39] was included in the present report
Geiss et al. [68]	Comparative study, different apheresis systems: Immunoadsorption systems versus non-immunoadsorption systems	Presented results as combined data
Banyai et al. [69]*	Case-series – different doses of drug therapy associated with apheresis	Apheresis system – immunoadsorption
Derfler and Goldammer [70]	Comparative study, three apheresis systems: Immunoadsorption, DSC, DALI	Presented results as combined data

continued on next page

Table 10: Excluded studies (cont'd)

Author	Type of study	Comments (reasons for exclusion)
Julius et al. [71]	Comparative study, three apheresis systems: HELP, DALI, Immunoadsorption – Therasorb	Did not present data on the level of lipids in the blood
Goldammer et al. [72]*	Case-series – different doses of drug therapy associated with apheresis	Apheresis system – Immunoadsorption (Therasorb)
Kopprasch et al. [73]	Cross-over study, two apheresis systems: HELP, DALI	Not specified if the patients included in the study were HMZ or HTZ. (asked for information - no response)
Schamberger et al. [74]	Comparative study, three apheresis systems: immunoadsorption, HELP, DSC, cascade-filtration	Included patients with FH and other HC patients.
Parhofer et al. [75]	Comparative study, two apheresis systems: immunoadsorption and HELP	Included HTZ FH patients and patients with severe combined hyperlipoproteinemia and did not specify the treatment received by each patient group
Yamamoto et al. [76]	Comparative study, two apheresis systems: DSC and double membrane filtration	Data were combined for both systems
Klingel et al. [77]	Cross-over study, two apheresis systems: HELP and Lipidfiltration (AC-1770 and EC-50)	Published the same article (results) in another journal. That study [33] was included in the present report
Julius et al. [38]	Comparative study, two apheresis systems: DALI and HELP	Did not provide data about lipoproteins reduction. Focused on impact of the devices on the coagulation system
Lepagne et al. [78]	Controlled study, DSC apheresis system	Used a normolipidemic control group. Focused on the impact of the apheresis system on oxidizability of atherogenic LDL subgroups.

* It was not clear from the abstact if this study is a case-series. It was retrieved to check the study design.

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